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How does symptom severity impact clinical outcomes of men with lower urinary tract symptoms after holmium laser enucleation or transurethral resection of the prostate?

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Introduction International Prostate Symptom Score (IPSS) is a validated outcome measure for the evaluation of patients with lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO). When treating patients with transurethral resection of the prostate (TURP) or holmium laser enucleation of the prostate (HoLEP), patient selection is key to achieve the best clinical outcome. Therefore, we analyzed how the severity of LUTS as determined by IPSS influenced postoperative functional outcomes.

Material and methods We conducted a retrospective, matched-pair analysis of 2,011 men who underwent HoLEP or TURP for LUTS/BPO between 2013–2017. We included 195 patients in the final analysis (HoLEP n = 97; TURP n = 98), who were matched for prostate size (50cc), age, and body mass index. Patients were then stratified by IPSS. Groups were compared for perioperative parameters, safety and short-term functional outcomes.

Results While preoperative symptom severity was a significant predictor of postoperative clinical improvement, patients who received HoLEP showed superior postoperative functional results with higher peak flow rates and 2-fold greater improvement in IPSS. In patients presenting with severe symptoms, we observed 3- to 4-fold less Clavien-Dindo grade ≥II and overall complications after receiving HoLEP compared to TURP.

Conclusions Patients with severe LUTS were more likely to experience clinically significant improvement after surgery than patients with moderate LUTS, and HoLEP showed superior functional outcomes than TURP. However, patients with moderate LUTS should not be denied surgery, but may warrant a more comprehensive clinical work-up.

Key Words: HOLEP ‹› TURP ‹› IPSS ‹› benign prostatic hyperplasia ‹› benign prostatic enlargement ‹› flow rate ‹› complications

INTRODUCTION

Both American Urological Association (AUA) and European Association of Urology (EAU) guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS) recommend using a questionnaire as objective outcome measure for initial assessment and monitoring in patients with LUTS secondary to benign prostatic obstruction (BPO). With the validated International Prostate Symptom Score (IPSS), a representative questionnaire consisting of seven questions, we classify patients into categories with mild (IPSS 0–7), moderate (IPSS 8–19) and severe symptoms (IPSS 20–35) [3]. Since IPSS was introduced in 1992 by Barry et al., it has become one of the most ubiquitously used questionnaires for assessing symptom severity in patients with LUTS/BPO [3]. Surrogate

parameters, such as IPSS, are easily assessible as part of the urological work-up and without additional strain for the patient. A decrease in IPSS of ≥3 must be achieved for new treatments to be considered effective by the patient [4]. Currently, patients receive either transurethral incision (TUIP), transurethral resection (TURP), endoscopic enucleation of the prostate (EEP) or even open prostatectomy (OP) for LUTS/BPO according to prostate size [1, 2].

With the introduction of holmium laser enucleation of the prostate (HoLEP), a size-independent method for surgical relief of LUTS has constantly challenged TURP as the surgical reference method [5–8]. HoLEP is effective in prostates of all sizes, and functional efficacy is even comparable to OP, but with a more favorable safety profile [6, 9]. HoLEP is at least equally efficient when compared to TURP, and even superior regarding perioperative morbidity [10]. As the prevalence of benign prostatic hyperplasia (BPH) increases with age, already half of the 50–60-year old male population present with the histological diagnosis of BPH upon autopsy, peaking up to 80% in men above the age of 80 years [11–14]. However, prostate size is not an unlimited predictor of LUTS and severe symptoms may be present in patients with smaller prostates [15]. Therefore, preoperative patient selection becomes crucial when offering surgical treatment for LUTS/BPO, and IPSS may be a viable instrument.

We therefore analyzed the impact of LUTS severity according to the IPSS on perioperative morbidity and mortality and postoperative functional outcomes for patients undergoing TURP or HoLEP for LUTS/BPO in a pair matched patient cohort.

MATERIAL AND METHODS

Patient population and study design

We performed a matched pair analysis of a total of 2,011 patients, who underwent HoLEP (n = 1,062) or TURP (n = 949) for LUTS/BPO from January 2013 to December 2017 at our institution. HoLEP or TURP were indicated in accordance with the current EAU guidelines on management of non-neurogenic male LUTS [2]. A computerized database was created for analyzing perioperative parameters, early functional outcomes, and safety profile for each procedure. Patients were matched according to prostate size of 50 cc, age (years), and body mass index (BMI) [10]. Patients were stratified into four groups according to symptom severity (IPSS) and procedure (Table 1). Patients with IPSS <8 points without surgical treatment were excluded from the final analysis. Only patients meeting those criteria, and in whom all the relevant information could be obtained, were included in the final analysis. Clinical and pathological information as well as perioperative data were used to describe the patient cohorts. Perioperative complications were analyzed in all groups and defined according to the modified Clavien-Dindo scale as any adverse event within 30 days of surgery [16].

All HoLEPs were performed by two experienced surgeons only, and in a three-lobe technique using VersaPulse® 100 W Holmium Laser (Lumenis Ltd., Yokneam, Israel) with a frequency of 53 Hz and a power setting of 1.2 kJ. Morcellation was performed using a mechanical tissue morcellator (R. Wolf, Piranha, Knittlingen, Germany). All TURPs were conducted with bipolar technique by four experienced surgeons, two of whom also performing the HoLEP procedures. According to our standard protocol a 24 Fr three-way Foley catheter was inserted after surgery and followed by 12 hours of continuous bladder irrigation with normal saline.

Statistical analysis

After the matching process, 98 patients for TURP and 97 patients for HoLEP were eligible for inclusion and final analysis. Statistical analysis was performed using SPSS V26.0 software (IBM SPSS Statistics, Version 26.0. Armonk, NY), and the multivariate logistic regression model was constructed using MedCalc 20 (MedCalc Inc., Ostend, Belgium). Results are given as median and interquartile range (IQR) for continuous variables and as percentage for categorial variables. Normal distribution of variables was determined with the Shapiro-Wilk test. Univariate analyses were performed using Fisher's exact test and T test for categorical variables, and Mann-Whitney U test for continuous variables. All reported p-values were two-sided and considered statistically significant if $p < 0.05$.

RESULTS

Patient characteristics

Demographic parameters are displayed in Table 1. In total, we included 195 patients and stratified them according to symptom severity and procedure. Therefore, patients significantly differed in IPSS score with a median IPSS in groups 1 and 2 of 15 (IQR 13–17) and 16 (IQR 12–18) versus groups 3 and 4 with 26 (IQR 23–29) and 25 (IQR 22–28), respectively ($p < 0.001$). In accordance, quality of life

(QoL) proved to be significantly better in groups 1 and 2 with a median of 3 (IQR 2–4) versus groups 3 and 4 with a median of 4 (IQR 4–5) for both groups, respectively (p <0.001). Most importantly, patients did not differ in prostate volume, age or BMI. Patients had a median prostate volume of 55 ml (IQR 41–69), 51 ml (IQR 41–60), 50 ml (IQR 45–59) and 50 ml (IQR 41–58) for groups 1–4, respectively (p = 673). Median age was 70 (IQR 60–75), 65 (IQR 58–72), 69 (IQR 61–75), and 65 (IQR 59–73), and median BMI was 25.4 (IQR 23.6–29.0), 25.1 (IQR 23.4–27.4), 25.7 (IQR 23.3–27.7), and 26.3 (24.3–28.0) for groups 1–4, respectively. There were no differences in maximum flow rate (Q_{max}), post void residual (PVR), preoperative hemoglobin level (Hb), total prostate-specific antigen (PSA), PSA density, American Association of Anesthesiologists (ASA) score, or percentage of patients presenting with an indwelling urinary catheter (IDC).

Perioperative assessment and functional outcomes

Table 2 shows the analysis of the perioperative data and short-term postoperative outcomes four weeks after surgery. We observed statistically significant differences in functional parameters and perioperative data between severity of symptoms (moderate vs severe IPSS) and operating modality (HoLEP vs TURP) between groups. All voiding parameters significantly improved after surgery. We observed a higher improvement of IPSS when comparing patients with moderate to severe preoperative

Table 1. *Demographic parameters*

Variables	Group 1 (HoLEP; moderate) n = 46	Group 2 (TURP; moderate) n = 52	p-value	Group 3 (HoLEP; severe) n = 51	Group 4 (TURP; severe) n = 46	p-value
IPSS						
Median	15	16	0.489	26	25	0.905
IQR	13–17	12–18		23–29	22–28	
QoL						
Median	3	3	0.917	4	4	0.530
IQR	2–4	2–4		4–5	4–5	
Prostate volume (cc)						
Median	55	51		50	50	0.673
IQR	41–60	41–60		45–59	41–58	
Age (years)						
Median	70	65		69	65	0.717
IQR	60–75	58–72		61–75	59–73	
BMI						
Median	25.4	25.1		25.7	26.3	0.679
IQR	23.6–29.0	23.4–27.4		23.3–27.7	24.3–28.0	
Q_{max} (ml/s)						
Median	10	10		12	10	0.603
IQR	7–15	9–14		8–16	8–15	
PVR (ml)						
Median	100	100		80	82	0.965
IQR	20–160	40–180		50–153	46–165	
Hb (g/dl)						
Median	15.0	14.9		15.0	14.6	0.598
IQR	14.2–16.1	14.1–15.6		14.5–15.7	14.0–15.9	
Total PSA (ng/ml)						
Median	3.1	2.3		3.3	2.3	0.169
IQR	1.4–5.4	1.4–3.5		1.9–5.0	1.5–3.6	
PSA density (ng/ml/cc)						
Median	0.06	0.05		0.07	0.04	0.104
IQR	0.03–0.10	0.03–0.07		0.04–0.10	0.03–0.08	
ASA score (%)						
≥III vs <III	23.8%	23.5%		23.5%	24.4%	0.693
N	(11)	(12)		(12)	(11)	
IDC (%)	11.9%	11.5%		11.8%	11.1%	0.779
N	(5)	(6)		(6)	(5)	

HoLEP – holmium laser enucleation of the prostate; TURP – transurethral resection of the prostate; IQR – interquartile range; BMI – body mass index; IPSS – International Prostate Symptom Score; QoL – quality of life; PVR – postvoid residual urine; Q_{max} – peak urinary flow rate; Hb – haemoglobin; PSA – prostate-specific antigen; ASA – American Society of Anaesthesiologists; IDC – indwelling urinary catheter

Table 2. *Perioperative and clinical outcomes 4 weeks after surgery*

Variables	Group 1 (HoLEP; moderate) n = 46	Group 2 (TURP; moderate) n = 52	p-value	Group 3 (HoLEP; severe) n = 51	Group 4 (TURP; severe) n = 46	p-value
Δ IPSS						
Median	8	6	**0.027**	16*	12**	0.025 *<0.001 **<0.001
IQR	5–12	4–10		8–20	6–17	
Δ QoL						
Median	2	2	0.133	3*	3**	0.664 *<0.001 **<0.001
IQR	1–3	1–3		2–4	3–4	
Δ Q_{max} (ml/s)						
Median	14	8	**0.022**	11	9.5	0.225
IQR	6–24	5–16		7–22	4–23	
Δ PVR (ml)						
Median	65	73		60	50	0.864
IQR	0–143	9–150		20–150	0–136	
Δ Hb (g/dl)						
Median	1.0	0.7		1.0	1.0	0.121
IQR	0.4–1.4	0.2–1.3		0.5–1.6	0.6–1.6	
Operating time (min)						
Median	59	54		63	59	0.237
IQR	50–72	46–67		52–74	49–74	
Operating efficiency rate (g/min)						
Median	0.60	0.41	**<0.001**	0.50	0.39	**0.002**
IQR	0.42–0.82	0.31–0.49		0.32–0.67	0.31–0.50	
Resected tissue (g)						
Median	41	20	**<0.001**	37	24	**<0.001**
IQR	25–49	19–30		30–50	18–30	
Resected tissue (%)						
Median	75	46	**<0.001**	76	48	**<0.001**
IQR	62–82	40–54		64–81	40–57	
Catheterization time (days)						
Median	2.0	2.0		2.0	2.0	0.202
IQR	2.0–2.0	2.0–3.0		2.0–2.0	2.0–3.0	
Hospitalization time (days)						
Median	3.0	3.0		3.0	3.0	0.137
IQR	3.0–3.0	3.0–4.0		3.0–3.0	3.0–4.0	

HoLEP – holmium laser enucleation of the prostate; IQR – interquartile range; BMI – body mass index; IPSS – International Prostate Symptom Score; QoL – quality of life; PVR – postvoid residual urine; Qmax – peak urinary flow rate; Hb – haemoglobin
Bold values indicate statistically significant p-values (p <0.05)

symptoms (Group 1 vs Group 3, p <0.001; Group 2 vs Group 4, p <0.001), while patients showed significantly higher improvement after HoLEP compared to TURP (Group 1 vs Group 2, p = 0.027; Group 3 vs Group 4, p = 0.025). Although median QoL improved significantly for all groups, improvement was higher in patients with severe symptoms (Group 1 vs Group 3, p <0.001; Group 2 vs Group 4, p <0.001). Median Q_{max} was also significantly improved throughout our patient cohort, patients with moderate symptoms receiving HoLEP profited the most with an improvement of 14 ml/s (IQR 6–24) versus Group 2 with an increase of 8 ml/s (IQR 5–16; p = 0.022), with no difference between modalities in patients suffering from severe LUTS. We found significant improvement of PVR, with no difference between all groups. We report no difference in postoperative hemoglobin drop between all groups. Although we observed no difference in total operating time, we found a significant difference in operating efficiency rate between modalities for Group 1 with 0.60 g/min (IQR 0.42–0.82) versus Group 2 with 0.41 g/min (IQR 0.31–0.49; p <0.001), and for Group 3 with 0.50 g/min (IQR 0.32–0.67) versus Group 4 with 0.39 g/min (IQR 0.31–0.50; p <0.001). Correspondingly, we have found absolute resected tissue to be higher in patients who were treated with HoLEP with 41 g (IQR 25–49) in Group 1 versus 20 g (IQR 19–30) in Group 2 (p <0.001), and 37 g (IQR 30–50) in Group 3 versus 24 g (IQR 18–30) in Group 4 (p <0.001). Also, percentage of resected tissue was higher in patients

Table 3. *Perioperative adverse events according to the Clavien-Dindo classification*

Variables	Group 1 (HoLEP; moderate) n = 46	Group 2 (TURP; moderate) n = 52	p-value	Group 3 (HoLEP; severe) n = 51	Group 4 (TURP; severe) n = 46	p-value
Overall AEs; N (%)	2 (4.3%)	7 (13.5%)	0.113	3 (5.9%)	9 (19.6%)	**0.029**
Clavien Dindo I	1 (2.2%)	3 (5.8%)		1 (2.0%)	2 (4.3%)	
Clavien Dindo II	1 (2.2%)	1 (1.9%)		0 (0.0%)	2 (4.3%)	
Clavien Dindo III	0 (0.0%)	3 (5.8%)		2 (3.9%)	5 (10.9%)	
CDC ≥II vs <II	1 (2.2%)	4 (7.7%)	0.122	2 (3.9%)	7 (15.2%)	**0.018**
Grade	Complication			Management		
I	Acute urinary retention after catheter removal (n = 7)			Bedside recatheterization		
II	Fever (n = 1) Clot retention (n = 3)			Antibiotics Clot evacuation		
III	Persistent hematuria (n = 4) Urethral stricture (n = 6)			Coagulation Urethral resection		

HoLEP – holmium laser enucleation of the prostate; TURP – transurethral resection of the prostate; AEs – adverse events
The following AEs were identified as perioperative complication: macrohematuria requiring prolonged bladder irrigation or surgical reintervention, clot retention, fever and urethral stricture requiring surgical intervention. Bold values indicate statistically significant p-values (p <0.05)

receiving HoLEP with 75% (IQR 62–82) in Group 1 versus 46% (IQR 40–54) in Group 2 (p <0.004), and 76% (IQR 64–81) in Group 3 versus 48% (IQR 40–57) in Group 4 (p <0.001). There was no difference in catheterization time or length of hospital stay when comparing LUTS severity, or surgical technique.

Perioperative complications

Overall, we observed 21 adverse events (AEs) in our study cohort (21/195, 10.8%). For describing and grading complications, the modified Clavien-Dindo classification (CDC) was used. In groups 1, 2, 3, and 4 respectively, 2 (4.3%), 7 (13.5%), 3 (5.9%), and 9 (19.6%) patients had at least one perioperative complication. While there was no significant difference in patients suffering from moderate LUTS, we report significantly more AEs in patients suffering from severe LUTS, who received TURP when compared to HoLEP. Overall, 5.9% of patients in Group 3 had an AE versus 19.6% in Group 4 (p = 0.029). We divided complications into minor (Clavien I) and major complications (Clavien II to V), requiring an intervention. While only 3.9% of patients in Group 3 suffered a major AE, we recorded 15.2% in Group 4 (p = 0.018) Complications and respective management are listed in detail in Table 3.

Probability of clinical improvement

Based on the multivariate logistic regression model, the probability of clinically significant improvement (i.e. improvement in IPSS of ≥3) was calculated. In the logistic regression model only severe preoperative IPSS was significantly associated with a clinically relevant improvement in IPSS of ≥3 (odds ratio = 4.08, 95% CI = 1.54–10.76, p = 0.005). The influence of the parameters Q_{max}, HoLEP, and severity of symptoms on the probability of a significant improvement is depicted in Figure 1.

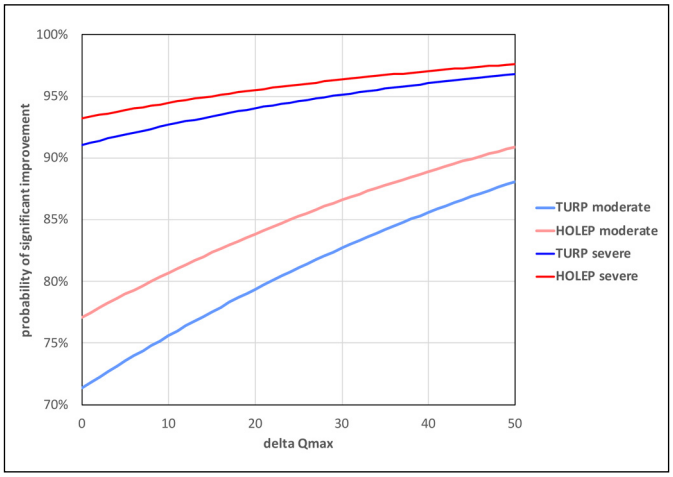

Figure 1. *Probability of clinically significant improvement in IPSS after surgery.*
The multivariate logistic regression model depicts the theoretical probability of clinically significant improvement (i.e. improvement in IPSS of ≥3) and influence of the parameters Qmax, preoperative symptom severity (expressed as IPSS), and treatment modality.
TURP – transurethral resection; HoLEP – holmium laser enucleation of the prostate; IPSS – International Prostate Symptom Score

DISCUSSION

With the introduction of an internationally standardized questionnaire to quantify LUTS in 1992 by Barry et al., commonly used outcome measure

became the integral part of the assessment of LUTS due to BPO [3]. Current guidelines aim to evaluate and recommend different treatment options mainly based on prostate size [1, 2]. Since its introduction, HoLEP has shown to be a size-independent method with efficacy and safety even outranking TURP and OP [7, 8, 9, 17]. Later the AUA symptom index evolved to the current version of IPSS, consisting of 7 questions and one QoL question, and could also be used to detect treatment efficacy [4]. As patients and practitioners alike, have a variety of treatment options to choose from when medical therapy for LUTS/BPO fails or is not feasible, using and further expanding the benefits of a standardized questionnaire to optimize treatment selection becomes mandatory. To minimize bias in the current analysis, patients were matched according to prostate size, age and BMI, and then stratified by procedure and symptom severity according to their respective IPSS. Apart from IPSS and QoL scores, our patient cohort did not differ in any of the preoperatively gathered parameters. However, reduced QoL may well correlate with an increase in IPSS and, therefore, symptom severity depicted by the IPSS itself [18, 19].

While preoperative LUTS medication may have had an impact on preoperative IPSS, we could recently show, that patients in fact presented with different preoperative LUTS medications at time of surgery, but were equally dissatisfied with symptom improvement [13]: patients, who received both α-blockers and 5-alpha reductase inhibitors (5-ARI) presented with significantly lower preoperative IPSS of 17 units vs 19 units in patients without previous LUTS medications or α-blocker monotherapy. On the one hand this may reflect efficacy of LUTS medications, but on the other hand it simultaneously shows the limitations of current pharmacotherapy, with only a difference of 2 units between groups, favoring a surgical approach for medication-refractory LUTS. Previous studies have shown that the decrease in IPSS of ≥3 must be achieved for LUTS/BPS medications to be considered effective and satisfying by the patient [4]. Therefore, we assessed whether severity of LUTS as determined by the IPSS had any impact on the improvement after surgery.

All patients improved significantly in functional parameters, regardless of operating technique. However, patients with higher preoperative IPSS showed a significantly stronger change after surgery, and – in general – were more likely to experience clinically significant improvement. When stratified by surgical technique, we report that improvement of IPSS favored HoLEP over TURP, regardless of preoperative symptom severity and corresponding to our previous data [20]. Improvement in QoL was significant throughout our patient cohort, with significantly stronger improvement in patients suffering from severe symptoms. This correlates with the current body of literature, that QoL scores adequately reflect and further objectify symptom severity in male patients suffering from LUTS [2, 18, 19]. While PVR similarly improved throughout our patient cohorts, postoperative improvement of Q_{max} was most pronounced in patients with moderate symptoms suffering from moderate LUTS after HoLEP. This may well be explained by two possibilities: patients suffering from moderate symptoms profit most from a more complete removal of prostate tissue, as can be seen with the higher total and resected tissue percentage favoring HoLEP, while the moderate – albeit clinically significant – improvement of Q_{max} in patients suffering from severe LUTS may be due to a higher prevalence of detrusor underactivity. Although the prevalence of detrusor underactivity increases with age and may thereby be contrasted by a decline of bladder outlet obstruction, our patient cohorts did not differ in age. However, urodynamic assessment was not routinely performed prior to surgery and therefore, we do not know exactly how many patients were also affected by detrusor underactivity. The less pronounced effect of minimally invasive prostate surgery may be due to an earlier onset of symptoms in patients with severe IPSS, regardless of the procedure [21–24]. As our patients were also matched by age and prostate size, patients with severe symptoms may have suffered from LUTS/BPO for an extended period of time and, therefore, detrusor contractility may need to be assessed over a longer follow-up period [15, 25, 26]. Although prostate volume progresses with age and the risk for developing LUTS/BPO increases with prostate size, we could show, that patients with comparable prostate sizes and demographic parameters can present with various degrees of LUTS [15, 25]. Furthermore, all patients had significantly improved voiding parameters after surgery. However, Elshal et al. could show that there was no significant difference in short-term (30 days) postoperative functional outcomes than after follow-up of 12 months [26].

Contrary to our initial analysis, in which total operating time favored TURP with a clinically insignificant median difference of 6.5 min, we found no difference between groups or operating technique when stratifying patients according to symptom severity [10]. However, HoLEP was significantly more efficient when taking into consideration that efficiency outcomes, total resected tis-

sue and percentage of resected tissue all favored HoLEP over TURP.

In total, 21 patients (21/195, 10.8%) suffered at least one postoperative complication defined by the modified CDC. When compared to the study by Mamoulakis et al., where overall CDC rate was 15.7%, our patient cohort had modest perioperative complications [16]. However, we observed significantly less postoperative complications in patients suffering from severe LUTS, who were treated with HoLEP compared to TURP. Also, complications were less severe, i.e. grade II CDC were recorded in the TURP cohort. However, patients suffering from moderate LUTS showed no difference in CDC when stratified by surgical technique. Even though we recorded four cases of persistent hematuria with need of coagulation, there was no need for peri- or postoperative blood transfusion. Additionally, postoperative hemoglobin drop was comparable between all groups and clinically insignificant. While CDC grade IV complications are generally rare, we report no grade IV or V CDC [26]. Thus, we found no life-threatening transurethral resection (TUR) syndrome in our patient cohort. However, TUR-syndrome is unlikely to appear during bipolar TURP, conducted in normal saline [27].

The retrospective design is a clear limitation of our study, and we only evaluated data gathered at a single tertiary referral center. Also, we did not include patients undergoing other laser treatment options, or TUIP for LUTS/BPO in our study. In addition, we only report short-term postoperative functional results and longer follow-up may be required for complete appraisal of functional outcomes and the safety profile. We also acknowledge, that preoperative IPSS alone may not be adequate to choose definitive treatment but it represents a valuable tool for both the initial clinical assessment and as a monitoring instrument after surgery. While patients with severe LUTS may have had a higher probability of clinical improvement after surgery, patients with moderate LUTS may profit from a more comprehensive clinical work-up. Nevertheless, we are confident in reporting our data showing that patients with different preoperative LUTS profiles profit from minimally invasive prostate surgery, while HoLEP may be more effective in patients with severe LUTS, as this may help urologists in determining the most promising treatment option.

CONCLUSIONS

In general, patients improved regardless of the surgical technique. However, patients suffering from moderate LUTS were less likely to experience significant postoperative symptom improvement, leading us to the following conclusions: 1) patients with moderate LUTS may profit from a more comprehensive clinical workup and may be offered further medication trials, 2) patients with moderate LUTS may be offered HoLEP instead of TURP as they may increase their chance of profiting from surgery due to a more rigorous enucleation, and 3) HoLEP is more effective and has a favorable safety profile in patients with severe LUTS compared to TURP.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

STATEMENT OF ETHICS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration of the World Medical Association and its later amendments or comparable ethical standards. In lieu of an ethical review board, authors state that for this type of study no formal consent is required, as all data were collected and analyzed anonymously.

DATA AVAILABILITY STATEMENT

All datasets generated for this study and supporting the findings of this study are included in the manuscript. The raw data of this study are available from the corresponding author upon reasonable request.

AUTHORS' CONTRIBUTION

Alexander Tamalunas: project development, data collection and analysis, manuscript writing
Melanie Schott: data collection and management, data analysis
Patrick Keller: data collection and management, data analysis
Michael Atzler: data collection and management
Benedikt Ebner: data collection and management
Alexander Buchner: data collection and management, data analysis
Christian Georg Stief: project development
Giuseppe Magistro: project development, data collection and analysis, manuscript writing

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